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PTC/US 96/09989INTERNATIONAL FILING DATE  
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## TITLE OF INVENTION

ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS

## APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☐ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ has been transmitted by the International Bureau.
  - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

## Items 13 to 18 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.  
A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
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U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO PTC/US 96/09989	ATTORNEY'S DOCKET NUMBER ARC 2426 CIP1
20. The following fees are submitted: <b>BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :</b> <input checked="" type="checkbox"/> Search Report has been prepared by the EPO or JPO ..... <b>\$930.00</b> <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... <b>\$720.00</b> <input type="checkbox"/> No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... <b>\$790.00</b> <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO ..... <b>\$1,070.00</b> <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ... .. <b>\$98.00</b>  <div style="text-align: right;"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></div>		<div style="border: 1px solid black; padding: 2px;"><b>CALCULATIONS PTO USE ONLY</b></div>
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CLAIMS	NUMBER FILED	NUMBER EXTRA
Total claims	26 - 20 =	6
Independent claims	2 - 3 =	0
Multiple Dependent Claims (check if applicable). <input type="checkbox"/>		<b>\$0.00</b>
<b>TOTAL OF ABOVE CALCULATIONS =</b>		<b>\$1,062.00</b>
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<b>TOTAL NATIONAL FEE =</b>		<b>\$1,062.00</b>
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input type="checkbox"/>		<b>\$0.00</b>
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<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>		
<b>SEND ALL CORRESPONDENCE TO:</b>		
<b>Christopher P. Rogers</b> <b>ALZA Corporation</b> <b>950 Page Mill Road</b> <b>(P.O. Box 10950)</b> <b>Palo Alto, CA 94303-0802</b> <b>(650) 496-8267</b>		<div style="text-align: center;">             SIGNATURE         </div> <div style="text-align: center;"> <b>Christopher P. Rogers</b>            NAME         </div> <div style="text-align: center;"> <b>36,334</b>            REGISTRATION NUMBER         </div> <div style="text-align: center;"> <b>11/17/97</b>            DATE         </div>

**ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS****TECHNICAL FIELD**

The present invention generally concerns a method and apparatus for the electrically assisted delivery of a therapeutic agent (e.g., a drug) through a body surface (e.g., intact skin) at increased efficiency. This invention is particularly applicable to the electrotransport of highly potent therapeutic agents which are to be delivered at small dosage levels.

**BACKGROUND OF THE INVENTION**

The present invention concerns in vivo methods and apparatuses for transdermal electrotransport delivery of therapeutic agents, typically drugs. Herein the terms "electrotransport", "iontophoresis" and "iontophoretic" are used to refer to methods and apparatus for transdermal delivery of therapeutic agents, whether charged or uncharged, by means of an applied electromotive force to an agent-containing reservoir. The particular therapeutic agent to be delivered may be completely charged (i.e., 100% ionized), completely uncharged, or partly charged and partly neutral. The therapeutic agent or species may be delivered by electromigration, electroosmosis or a combination of these processes. Electroosmosis has also been referred to as electrohydrokinesis, electro-convection, and electrically-induced osmosis. In general, electroosmosis of a therapeutic species into a tissue results from the migration of solvent, in which the species is contained, as a result of the application of electromotive force to a reservoir containing the therapeutic species.

As used herein, the terms "electrotransport", "iontophoresis" and "iontophoretic" refer to (1) the delivery of charged drugs or agents by electromigration, (2) the delivery of uncharged drugs or agents by the process of electroosmosis, (3) the delivery of species by transport processes which include an electroporation step (See, e.g., Weaver et al. U.S. Patent 5,019,034), (4) the delivery of charged drugs or agents by the combined processes of electromigration and electroosmosis, and/or (5) the delivery of

1 a mixture of charged and uncharged drugs or agents by the combined  
2 processes of electromigration and electroosmosis, combinations of the above  
3 processes to deliver either or both of charged or uncharged species.

4 Iontophoretic devices for delivering ionized drugs through the skin  
5 have been known since the early 1900's. See for example, Deutsch U.S.  
6 Patent 410,009. In presently known electrotransport devices, at least two  
7 electrodes or electrode assemblies are used. Both electrodes/electrode  
8 assemblies are disposed so as to be in intimate electrical contact with some  
9 portion of the skin of the body. One electrode, called the active or donor  
10 electrode, is the electrode from which the ionic substance, agent,  
11 medicament, drug precursor or drug is delivered into the body through the  
12 skin by iontophoresis. The other electrode, called the counter or return  
13 electrode, serves to close the electrical circuit through the body. In  
14 conjunction with the patient's skin contacted by the electrodes, the circuit is  
15 completed by connection of the electrodes to a source of electrical energy,  
16 e.g., a battery. For example, if the ionic substance to be delivered into the  
17 body is positively charged, then the positive electrode (the anode) will be the  
18 active electrode and the negative electrode (the cathode) will serve to  
19 complete the circuit. If the ionic substance to be delivered is negatively  
20 charged, then the cathodic electrode will be the active electrode and the  
21 anodic electrode will be the counter electrode.

22 As is discussed above, electrotransport delivery devices can be used  
23 to deliver uncharged drugs or agents into the body, e.g., transdermally. This  
24 is accomplished by a process called electroosmosis. Electroosmosis is the  
25 (e.g., transdermal) flux of a liquid solvent (e.g., the liquid solvent containing  
26 the uncharged drug or agent) which is induced by the presence of an electric  
27 field imposed across the skin by the donor electrode.

28 Electrotransport electrode assemblies/devices generally include a  
29 reservoir or source of the beneficial agent or drug (preferably an ionized or  
30 ionizable species or a precursor of such species), which is to be delivered  
31 into the body by electrotransport. Examples of such reservoirs or sources

1 include a pouch as described in Jacobsen U.S. Patent 4,250,878, a pre-  
2 formed gel body as disclosed in Webster U.S. Patent 4,382,529 and Ariura,  
3 et al. U.S. Patent 4,474,570 and a receptacle containing a liquid solution as  
4 disclosed in Sanderson, et al. U.S. Patent 4,722,726. Such drug reservoirs  
5 are connected to the anode or the cathode of an electrotransport device to  
6 provide a fixed or renewable source of one or more desired species or  
7 agents. Electrical current is typically applied to the reservoir by means of a  
8 current distributing member, which may take the form of a metal plate, a foil  
9 layer, a conductive screen, or a polymer film loaded with an electrically  
10 conductive filler such as silver or carbon particles. The current distributing  
11 member, including any appropriate connectors and associated connective  
12 conductors such as leads, and the reservoir comprise an electrode assembly  
13 herein.

14 The prior art has recognized that "competitive" ionic species having  
15 the same charge (i.e., the same sign) as the drug ions being delivered by  
16 electrotransport have a negative impact on electrotransport drug delivery  
17 efficiency. The efficiency (E) of electrotransport delivery of a particular  
18 species is defined herein as the rate of electrotransport delivery of that  
19 species per unit of applied electrotransport current (mg/mA-h). The prior art  
20 further recognized that competitive ionic species were inherently produced  
21 during operation of these devices. The competitive species produced are  
22 dependent upon the type of electrode material which is in contact with the  
23 drug solution. For example, if the electrode is composed of an  
24 electrochemically inert material (e.g., platinum or stainless steel), the  
25 electrochemical charge transfer reaction occurring at the electrode surface  
26 tended to be water electrolysis since water is the overwhelmingly preferred  
27 liquid solvent used in electrotransport drug solutions. Water electrolysis  
28 produces competing hydronium ions at the anode (in the case of cationic  
29 electrotransport drug delivery) and competing hydroxyl ions at the cathode  
30 (in the case of anionic electrotransport drug delivery). On the other hand, if  
31 the electrode is composed of an electrochemically oxidizable or reducible

1 species, then the electrode itself is oxidized or reduced to form a competitive  
2 ionic species. For example, Untereker et al U.S. Patent 5,135,477 and  
3 Petelenz et al U.S. Patent 4,752,285 recognize that competitive ionic species  
4 are electrochemically generated at both the anode and cathode of an  
5 electrotransport delivery device. In the case of an electrotransport delivery  
6 device having a silver anodic donor electrode, application of current through  
7 the silver anode causes the silver to become oxidized ( $\text{Ag} \rightarrow \text{Ag}^+ + \text{e}^-$ )  
8 thereby forming silver cations which compete with the cationic drug for  
9 delivery into the skin by electrotransport. The Untereker and Petelenz  
10 patents teach that providing a cationic drug in the form of a halide salt  
11 causes a chemical reaction which removes the "competing" silver ions from  
12 the donor solution (i.e., by reacting the silver ions with the halide counter ion  
13 of the drug to form a water insoluble silver halide precipitate;  $\text{Ag}^+ + \text{X}^- \rightarrow$   
14  $\text{AgX}$ ), thereby achieving higher drug delivery efficiency. In addition to these  
15 patents, Phipps et al PCT/US95/04497 filed on April 7, 1995 teaches the use  
16 of supplementary chloride ion sources in the form of high molecular weight  
17 chloride resins in the donor reservoir of a transdermal electrotransport  
18 delivery device. These resins are highly effective at providing sufficient  
19 chloride for preventing silver ion migration, yet because of the high molecular  
20 weight of the resin cation, the resin cation is effectively immobile and hence  
21 cannot compete with the drug cation for delivery into the body.

22 The prior art has long recognized that the application of electric  
23 current through skin causes the electrical resistance of the skin to decrease.  
24 See, for example, Haak et al U.S. Patent 5,374,242 (Figure 3). Thus, as the  
25 electrical resistance of the skin drops, lower voltages are needed to drive a  
26 particular level of electrotransport current through the skin. This same  
27 phenomenon is observed in a technique referred to as "electroporation" of  
28 the skin. See Weaver et al U.S. Patent 5,019,034. Electroporation involves  
29 the application of short, high voltage electrical pulses to produce what is  
30 characterized as a transient (e.g., decreasing to normal levels in 10 to 120  
31 sec. for excised frog skin) increase in tissue permeability. Electroporation is

1 also characterized by the creation of pores in lipid membranes due to  
2 reversible electrical breakdown. Electroporation does not, itself, deliver any  
3 drug but merely prepares the tissue thereby treated for delivery of drug by  
4 any of a number of techniques, one of which is iontophoresis.

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### **DISCLOSURE OF THE INVENTION**

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The present invention arises from the discovery that, under specified conditions of applied electrotransport current density (generally expressed in units of microamperes/cm<sup>2</sup> herein) and application time, the electrotransport transdermal drug delivery efficiency is enhanced. Electrotransport drug delivery efficiency,  $E$ , is defined as the rate of transdermal electrotransport delivery (mg/h) per unit of applied electrotransport current (mA), and expressed in units of milligrams of agent (e.g., drug) delivered per milliamp-hour of applied electric current (mg/mAh). Electrotransport delivery efficiency, in some aspects of its meaning, is analogous to transport number. Transport number is a unitless quantity, less than one, indicating the fractional charge carried by a particular ionic species, e.g., a drug or agent, during electrotransport delivery. Electrotransport delivery efficiency, as defined herein, is more broadly applicable to include the transport of uncharged species and is more reflective of the scope of the invention.

The enhancement of the skin's electrotransport efficiency has been found to be non-transitory, i.e., to last for at least several minutes to several hours or longer after application of this invention. This invention induces (e.g., through a pre-treatment or pre-application step in which species are delivered) a high efficiency drug-transmissive state in the skin to which it is applied. The induced, high efficiency state continues and can be utilized to deliver drug or other therapeutic agent transdermally via electrotransport with increased efficiency. In usual circumstances, this will permit delivery of drug with more precise control and at a lower current. This phenomenon has only been found in the transdermal delivery of drug or agent through intact living

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1 skin or tissue, (i.e., in vivo) and is not exhibited in dead skin (i.e., excised  
2 skin through which species are electrotransported in vitro).

3 Generally speaking, this invention involves delivery of a charged  
4 species at or above a pre-determined threshold current density  $I_c$  for at least  
5 a predetermined period of time  $t_c$  (e.g., for a predetermined pulse width)  
6 through the site of drug delivery, e.g., intact skin. In this manner, the treated  
7 skin exhibits a statistically significant, non-transitory increase in drug delivery  
8 efficiency relative to skin which has not been so treated. Generally  
9 speaking, utilization of this invention will significantly increase the drug/agent  
10 delivery efficiency and reduce or eliminate efficiency variability of the skin  
11 segment which is so treated. Since electrotransport delivery efficiency  
12 remains elevated or less variable after utilization of this invention (relative to  
13 untreated skin), utilization of this invention permits the delivery of drug or  
14 agent through intact skin by electrotransport with increased control and  
15 efficiency.

16 Briefly, in one aspect, the present invention is a method of  
17 electrotransport drug or agent delivery through a body surface involving the  
18 steps of:

19 delivering ionic species by electrotransport at a sufficient  
20 current density and over a sufficient period which will change or  
21 convert the transport efficiency of the body surface through which the  
22 ionic species is delivered to a non-transitory state of higher species  
23 delivery efficiency; and thereafter

24 delivering drug or agent through the body surface while in its  
25 high efficiency state.

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27 In a preferred practice, current density and species delivery time are  
28 selected to maintain the higher efficiency species delivery state of the body  
29 surface. This invention also includes the preferred practice of intentionally  
30 renewing the highly efficient species delivery state so as to optimize drug  
31 delivery efficiency if drug or agent delivery conditions are used which do not



1 periodically renew it. In another preferred practice, the present invention is  
2 utilized to deliver drug or agent transdermally, i.e., through intact skin. In yet  
3 a further preferred practice, the present invention is used to deliver drug or  
4 agent through intact, live, human skin.

5 In the practice of this invention, the precise current density and  
6 treatment time period needed to convert untreated skin to a highly  
7 transmissive state have been found to be fairly specific to the drug or  
8 therapeutic agent to be delivered. However, for the electrotransport delivery  
9 of analgesics, which have been the primary focus of this invention, a  
10 treatment of the body site through which drug is to be delivered for a time  
11 period of at least 5 msec, and preferably at least 10 msec, at a current  
12 density of at least about 40  $\mu\text{A}/\text{cm}^2$ , preferably at least about 50  $\mu\text{A}/\text{cm}^2$  and  
13 most preferably at least about 70  $\mu\text{A}/\text{cm}^2$  appears to convert the body site so  
14 treated to a highly drug transmissive state as defined in this invention. This  
15 invention arises because of the discovery that electrotransport delivery  
16 efficiency is highly dependent (i.e., it is non-constant) at current densities in  
17 the range of about 0 to about 30  $\mu\text{A}/\text{cm}^2$ , is moderately dependent upon  
18 current density in the range of about 40 to about 70  $\mu\text{A}/\text{cm}^2$  and is relatively  
19 independent of current density at current densities in excess of about 70  
20  $\mu\text{A}/\text{cm}^2$ . This unexpected change in efficiency (in theory, efficiency is not  
21 predicted to change with increasing current density) permits transdermal  
22 electrotransport delivery of drug with significantly enhanced efficiency.

23 A second unexpected result is achieved in the practice of the present  
24 invention, i.e., the change of the skin to the higher efficiency transmissive  
25 state is non-transitory with the skin remaining in the higher, and more stable,  
26 efficiency state for minutes to hours after the initial transformation, even in  
27 cases where the subsequently applied electrotransport current density is  
28 lowered to a level below  $I_c$  or turned off, completely. In other words, when  
29 the skin site has been converted to a highly efficient agent transmissive state  
30 by applying a pulsing electric current, the current pulses having a sufficient  
31 magnitude to provide a current density at or above the critical current density

1  $I_c$ , and preferably over pulse widths of at least 5 msec reduction in applied  
2 electrotransport current (and therefore current density) does not cause the  
3 skin to immediately return to its initial, lower efficiency state. This  
4 observation respecting in vivo drug delivery is critically important to  
5 electrotransport system design.

6 The term "non-transitory" as used herein, when referring to the high  
7 efficiency electrotransport agent delivery state, means of sufficient length to  
8 permit drug to be delivered to achieve a therapeutic effect. Thus, for  
9 example, a relatively inexpensive ionic species may be used to trigger  
10 conversion of, e.g., a skin site, to a highly efficient and more stable ionic  
11 species delivery state, and thereafter relatively more expensive drug or agent  
12 may be delivered at greater efficiency and stability by electrotransport.  
13 Where the drug or agent is inexpensive, it may be used to convert the body  
14 delivery site to the highly efficient and more stable state, and thereafter may  
15 be delivered with greater efficiency, i.e., at lower current density and at  
16 greater stability.

17 The term "high/higher efficiency state" as used herein means  
18 conversion of any particular body or skin site to a state in which drug or  
19 agent delivery is at least 10% (preferably 20%) more efficient than the same  
20 skin site prior to conversion in accordance with this invention. Generally, the  
21 parameter which will be most reflective of this efficiency increase is the  
22 electrotransport delivery efficiency measured in milligrams of drug delivered  
23 per milliamp-hour of applied electrotransport current.

24 The term "more stable efficiency" as used herein means conversion of  
25 a body surface site from a state of more variable electrotransport agent  
26 delivery efficiency to one of less variability by exposure of the body site to a  
27 current density above the critical current density  $I_c$  for a time period longer  
28 than the critical time,  $t_c$ . Critical current density for purposes of increased  
29 stability, has been found to be as low as about 40  $\mu A/cm^2$ .

30 In a preferred practice of this invention, it is desirable to be able to  
31 change, precisely, drug dosage after the body site has been converted to a

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1 highly efficient drug or agent delivery state. In accordance with this  
2 invention, total drug or agent delivered (i.e., dosage) may be adjusted while  
3 maintaining the required current density to retain the most efficient and  
4 stable state, i.e., independent of average current applied by the alternatives  
5 of: (a) in a pulsed output electrotransport system, adjustment of device duty  
6 cycle while maintaining average current density above the critical current  
7 density; (b) in an electrotransport device employing a pulsed output,  
8 maintaining constant peak current and pulse width while adjusting pulse  
9 frequency to adjust total drug or agent delivered, or (c) the intentional  
10 inclusion in and delivery from an "in line" (i.e., to deliver drug) component  
11 or subassembly of an electrotransport device of competitive co-ions not  
12 having a therapeutic effect converts the system to a stable drug flux at a  
13 current density above the critical current density. Delivery of competitive co-  
14 ions, for a given current, in addition to the drug or agent ions, provides  
15 adequate current density but permits controlled modification of the quantity of  
16 therapeutic agent delivered. Delivery of competitive co-ions from, e.g., the  
17 drug reservoir, also reduces potentially expensive and potent total drug or  
18 agent delivered.

19 Another way to use an inexpensive ionic species to trigger the skin  
20 conversion is to utilize a reverse polarity system. One example of such a  
21 system would first drive the anionic drug counter ion from the donor reservoir  
22 and the cationic substance from the counter reservoir for the time required to  
23 convert the skin to a high efficiency state and then reverses polarity, thereby  
24 moving the drug cation into the skin.

25 In one practice of this invention, the highly potent analgesic drug,  
26 fentanyl, is transdermally delivered via electrotransport at very low current  
27 density under conditions at which fentanyl delivery tends to be unstable, i.e.,  
28 to exhibit unacceptable drug delivery efficiency variability. Addition of a  
29 chloride salt, e.g., sodium chloride, to the electrode assembly drug reservoir  
30 provides sufficient co-deliverable, competitive ion (i.e.  $\text{Na}^+$ ) to stabilize  
31 fentanyl delivery. In this manner, fentanyl efficiency variability also is

1 reduced or eliminated. These and other aspects of this invention will be  
2 discussed below.

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#### **BRIEF DESCRIPTION OF THE DRAWINGS**

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A better understanding of the present invention, as well as other objects and advantages thereof, will become apparent upon consideration of the following modes for carrying out the invention especially when taken with the accompanying drawings, wherein:

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FIG. 1 is a graph of transdermal electrotransport drug delivery efficiency (E) versus applied electrotransport current density ( $I_d$ ) for in vivo delivery of fentanyl;

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FIG. 2 is a graph of electrotransport current versus time, showing three pulsed current waveforms having differing duty cycles;

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FIG. 3 is an exploded perspective view of a transdermal electrotransport drug delivery device which can be used in accordance with the method of the present invention.

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FIG. 5 is a graph of mean serum fentanyl concentration versus time, showing how initial electrotransport administered doses increase subsequent fentanyl delivery through a 24 hour period;

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FIG. 6 is a graph of average serum fentanyl concentration, as a function of time, for applied electrotransport current densities of 10, 20 and 40  $\mu\text{A}/\text{cm}^2$ ;

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FIG. 7 is a graph of serum fentanyl concentration versus time for delivery of fentanyl at pulsing frequencies of 1, 10, and 625 Hz; and

FIG. 8 is a graph of serum goserelin concentration versus time, for applied electrotransport current densities of 50 and 100  $\mu\text{A}/\text{cm}^2$ .

### MODES FOR CARRYING OUT THE INVENTION

The present invention is based upon the discovery that the efficiency (E) of transdermal electrotransport agent (e.g., drug) delivery is, at least at lower applied electrotransport current densities, dependent on the applied electrotransport current density ( $I_d$ ). This phenomenon is illustrated graphically in FIG. 1. Specifically, we have discovered that when electrotransport current densities at or above a critical current density level,  $I_c$ , are applied to the skin of living animals for a sufficient period of time, at least as long as a critical period of time  $t_c$  on the order of several milliseconds, the electrotransport drug delivery efficiency (E) increases and becomes independent of the level of applied electrotransport current density. It is important to note that the variable electrotransport delivery efficiency effect is a limited exception to the widely reported principle that transdermal electrotransport drug flux is dependent (i.e., linearly dependent) upon the level of applied electrotransport current. Our discovery is that this principle is only true at current densities at or above a critical current density level  $I_c$ . Thus, we have discovered that, at applied current densities below the critical current density level  $I_c$ , the rate of electrotransport drug delivery per unit of applied electrotransport current is not constant as has been previously assumed. Not only is the electrotransport drug delivery efficiency (E) variable at lower current densities, it is also lower than at current densities above the critical level  $I_c$ . Thus, at applied current densities below  $I_c$ , the electrotransport delivery is less efficient in that more electrotransport current must be applied to deliver a predetermined amount of drug. A still further aspect of our discovery is that the interpatient variability in transdermal electrotransport efficiency is lower at applied current densities above the critical level  $I_c$  and higher at applied current density levels below the critical level  $I_c$ .

In general, the critical current density level  $I_c$  for human skin is in the range of about 40 to 100  $\mu\text{A}/\text{cm}^2$ , although the critical level  $I_c$  will vary somewhat depending upon (i) the particular drug being delivered, (ii) the

1 particular patient being treated, and (iii) the particular skin location of the  
2 patient wearing the electrotransport device. Typically, a current density at or  
3 above the critical level  $I_c$  need only be applied for several milliseconds to  
4 several seconds before the skin enters the high efficiency drug transfer state.  
5 However, applied current densities below the critical level  $I_c$  are unable to  
6 transform the skin into the high efficiency transfer state, even when these  
7 low level current densities are applied for extended periods of time (e.g., up  
8 to several hours application). This transformation of the skin to a higher  
9 efficiency delivery state occurs only in living animals and does not occur with  
10 excised skin taken from living or dead animals, i.e., the skin transformation  
11 has not been found to occur when in vitro flux studies were run.

12       Once the skin has been transformed into the high efficiency transfer  
13 state, it tends to remain in that state for an extended period of time (e.g., up  
14 to 24 hours) even if no further electrotransport current is thereafter applied to  
15 the skin or if only low level current densities (i.e., current densities less than  
16 the critical level  $I_c$ ) are thereafter applied to the skin. This result is illustrated  
17 in FIG. 5 and is discussed below. The "transformed" skin is in general only  
18 those skin sites which are in contact with the donor and counter  
19 electrodes/reservoirs of the electrotransport delivery device and through  
20 which skin sites the applied current has been passed. Thus, if a skin site on  
21 the upper arm of a patient has been transformed by application of  
22 electrotransport current densities at or above the critical level  $I_c$ , the skin on  
23 the lower (same) arm, the legs, torso or other arm of the patient does not  
24 become transformed. The skin transformation of this invention is a localized  
25 phenomenon which is limited to those portions of the skin to which the donor  
26 and counter electrodes/reservoirs are attached. Since the skin at the  
27 counter electrode site also is converted to the higher efficiency delivery state,  
28 methods and devices for delivering agents from the "donor" and "counter"  
29 electrodes or both electrodes (e.g., by alternating current polarity) are within  
30 the scope of this invention.

Our discovery is particularly critical in those transdermal electrotransport drug delivery regimens wherein the drug is delivered at two (or more) different dosing levels, one dosing level being administered at a current density below the critical level  $I_c$  and another dosing level being administered at a current density above the critical level. For example, many drugs are adapted to be administered at a low dose baseline rate for extended periods, the baseline rate being interrupted periodically by periods of higher dosing. Examples of drugs which are administered in this fashion include (1) analgesics, such as fentanyl and sufentanil, which are administered at a low baseline level to treat (e.g., chronic) pain and which are periodically delivered at higher doses to treat more severe episodes of pain; (2) anti-emetics, such as the 5HT<sub>3</sub> receptor antagonists ondansetron and granisetron, which are administered continuously at low levels (e.g., during weeks over which a patient is undergoing chemotherapy) and which are periodically administered at higher dosing levels (i.e., during the actual chemotherapeutic administration); (3) anti-epileptics, such as phenytoin, which are delivered continuously at low baseline levels and periodically at higher levels when the patient is undergoing an epileptic seizure; and (4) anti-diabetic drugs, such as insulins, which can be delivered continuously at low baseline levels and periodically (e.g., around meal times) at higher levels. The problem encountered with this type of transdermal electrotransport drug administration is that after the drug is administered at the higher dosing rate (with the applied current density above the critical level,  $I_c$ ), when the applied electrotransport current is readjusted to apply the original lower baseline level, the transdermal electrotransport drug flux does not return to the same baseline level. The drug flux instead falls to a level somewhere between the original baseline rate and the high dosing rate, because the skin has been transformed into a higher efficiency drug delivery state. For example, if the efficiency is enhanced by a factor of two, after the skin has experienced a current density above the critical current density, and then the current is lowered to the original baseline current, the drug

1 delivery rate would be twice that experienced before the transformation. The  
2 higher baseline rate could result in a drug overdose if the electrotransport  
3 system does not compensate for this shift in efficiency. To eliminate this  
4 problem, the electrotransport system should reduce the current applied (e.g.,  
5 by approximately a factor of two) after the skin has experienced a current  
6 density greater than  $I_c$ . With reference to FIG. 1, data point 2 is a likely  
7 efficiency that would be experienced at the drug delivery site were current  
8 (and therefore current density) reduced after exposure of the body site to a  
9 current density at or above  $I_c$  for at least a period of time  $t_c$ . At data point  
10 "2", the electrotransport agent delivery efficiency is higher than the agent  
11 delivery efficiency which was experienced initially (i.e., before exposure to a  
12 current density above  $I_c$ ) at the current density of  $20 \mu\text{A}/\text{cm}^2$ .

13 A more elegant approach to this problem is to apply a pulsed  
14 electrotransport current to the skin, the pulsing current having a magnitude  
15 above the critical level  $I_c$ , and to modify the duty cycle of the pulses to  
16 increase or decrease the amount of drug delivered. The term "duty cycle"  
17 as used herein is the ratio of "on" time interval to the period of time of one  
18 cycle (i.e., the ratio of the pulse-duration time to the pulse-period) and is  
19 usually expressed as a percent. For example, if a device is "on" for 500 ms  
20 of a 1 sec cycle, then the device is operating in a 50% duty cycle. In this  
21 practice of the invention, the magnitude of the current pulses is selected in  
22 view of the known area of the surface from which drug is delivered, thereby  
23 defining a fixed and known current density (i.e., the ratio of current to the  
24 area from which current flows). Thus, if it is decided, based upon application  
25 of the above principles, that a specific maximum current for a given anode  
26 surface area e.g.,  $I_{\text{max}}$ , will provide the enhanced efficiency drug delivery  
27 discussed above, then by increasing or decreasing the duty cycle, the  
28 amount of drug delivered at the high efficiency state can be increased or  
29 decreased without causing the applied current density to change. In  
30 choosing the parameters of drug delivery if using this approach, the  
31 magnitude of the current pulses is selected so that the resulting current



1 density transforms the skin into the high efficiency state and the duty cycle  
2 of the current pulses is altered to adjust the drug delivery rate (i.e., a low  
3 dose of drug is administered by a high density (i.e., greater than or equal to  
4  $I_c$ ) pulsing current having a low duty cycle and a high dose of drug is  
5 administered by the same magnitude current density but being pulsed at a  
6 longer pulse width corresponding to a higher duty cycle.

7 This aspect of the invention is more specifically illustrated in Fig. 2  
8 where waveforms for three different pulsing electrotransport currents of the  
9 same frequency are shown. In FIG. 2 time is illustrated on the horizontal  
10 axis, while current amplitude is illustrated on the vertical axis. The three  
11 current waveforms shown in FIG. 2 all have the same magnitude, and hence  
12 the same maximum applied current density  $I_{max}$  for an electrotransport  
13 delivery device of any one size. This particular current density  $I_{max}$  is greater  
14 than the critical current density level  $I_c$ . The three current waveforms have  
15 differing duty cycles, which is the percentage of time during which the  
16 current is applied. The three waveforms have duty cycles of 75% (top  
17 waveform), 50% (middle waveform) and 25% (bottom waveform). Thus, the  
18 25% duty cycle waveform delivers drug transdermally by electrotransport at  
19 about one-half the dosing level of the 50% duty cycle waveform and about  
20 one-third the dosing level of the 75% duty cycle waveform. All three  
21 waveforms administer drug transdermally by electrotransport through skin  
22 which is transformed into the high efficiency transfer state by reason of  $I_{max}$   
23 being greater than  $I_c$ .

24 In a further practice of this invention, the pulsing frequency of a  
25 pulsed current waveform is adjusted to control the overall quantity of drug  
26 delivered while holding the pulse width constant and maintaining the  
27 magnitude of current pulses at or above  $I_c$ . In this manner, current density is  
28 maintained at or above the level which transforms the skin into the high  
29 efficiency state. Exemplary of this, a device employing a pulsed current  
30 waveform having current pulses with a magnitude of 0.2 mA, a pulse width  
31 of 10 msec, and a frequency of 10 Hz will deliver roughly half as much drug

1 as the same device run at a frequency of 20 Hz. Given a constant drug  
2 delivery area, e.g., of an electrode assembly, the applied current densities of  
3 these two devices is the same and is above the high efficiency critical level  $I_c$   
4 so that both devices deliver drug transdermally by electrotransport with  
5 higher efficiency and lower variability compared to devices which apply  
6 electrotransport current at current densities below the critical level  $I_c$ . From  
7 these two examples of the invention, one skilled in this art will appreciate  
8 that a combination of frequency and duty cycle may be used to alter the rate  
9 of drug delivery while maintaining the maximum applied current density,  $I_{max}$ ,  
10 above  $I_c$ . FIG. 4 shows the waveforms for a device operated to have a  
11 constant 9 msec pulse width, the frequency for a device operated according  
12 to the lower waveform being one-half that of a device operated according to  
13 the upper waveform (i.e., 50 Hz versus 100 Hz).

14 As is noted above, agent delivery efficiency is increased by exposure  
15 of the site to a current density at or above  $I_c$  and for a time period equal to  
16 or greater than a critical time,  $t_c$ . Generally speaking, for a pulsing  
17 electrotransport device, the pulse width must equal or exceed  $t_c$ . Thus,  $t_c$ , in  
18 a practice of this invention using pulsed current electrotransport devices and  
19 for delivery of fentanyl, falls between about 0.5 msec and 30 msec. It is  
20 believed that the minimum pulse width to cause transformation to the higher  
21 efficiency state is about 10 msec for fentanyl.

22 Table 1 shows data which support the above observation. Table 1  
23 shows drug delivery efficiency data for a device programmed to run at  
24 frequencies of 1 Hz, 10 Hz and 625 Hz. A 31% duty cycle was employed.

25

26

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TABLE 1

Frequency Hz	Pulse Width	Rate of Fentanyl Delivery $\mu\text{g/hr.}$	
		Without Bolus Treatment	After Bolus Treatment*
625	0.5 msec	7	34
10	31 msec	52**	52**
1	310 msec	48**	48**

\* "Bolus Treatment" means a direct current bolus delivery of fentanyl for a period of 30 minutes at a current density of  $0.1\text{mA/cm}^2$ .

\*\* The numbers in these two columns are the same because even at a pulse width as short as 31 msec, the skin site had already transformed to its highly efficient state.

Table 1 also indicates that fentanyl delivery is significantly lower at a high pulsing frequency of 625 Hz compared to the lower pulsing frequencies of 1 and 10 Hz. This phenomenon is called capacitive loss, which loss becomes greater as pulsing frequency is increased at a given duty cycle. Capacitive loss results because a portion of each pulse is consumed by the process of charging the skin without delivering drug. The shorter the pulse width (and hence the higher the pulsing frequency), the greater (relatively speaking) the capacitive loss for each pulse. Table 1 also shows that until a critical pulse width is achieved, regardless of frequency, no transformation of the body site agent delivery efficiency occurs.

Pulsed current electrotransport devices are well known in the art. Such devices are described in numerous technical articles and the patent literature including Bagniefski et al. "A Comparison of Pulsed and Continuous Current Iontophoresis", Journal of Controlled Release, 113-122, (1090); McNichols et al., U.S. patent 5,047,007; Sibalís U.S. Patent 5,135,478; R. Burnette et al. "Influence of Constant Current Iontophoresis on the Impedance and Passive  $\text{Na}^+$  Permeability of Excised Nude Mouse Skin",

1 77 J.Pharmaceutical Sciences 492 (1988); Pikal et al, "Study of the  
2 Mechanisms of Flux Enhancement Through Hairless Mouse Skin by Pulsed  
3 DC Iontophoresis," 8 Pharmaceutical Research 365 (1991).

4 Another method of transdermally delivering a therapeutic agent (e.g.,  
5 a drug) by electrotransport at an applied current density at or above the  
6 critical level  $I_c$  but at a lower dosing/delivery rate (i.e., a rate which requires a  
7 current lower than that achieved when applying a current sufficient to  
8 achieve a current density of at least  $I_c$ ) involves the intentional introduction of  
9 competitive ions having the same (i.e., same polarity) charge as the  
10 therapeutic agent ions. This approach, under the specific conditions  
11 described, permits drug dosage control as well as providing enhanced  
12 stability and enhanced efficiency of electrotransport of therapeutic agent.  
13 This approach is generally discouraged in the patent literature because it  
14 otherwise tends to reduce drug delivery efficiency. This aspect of this  
15 invention is particularly applicable to electrotransport delivery of those drugs  
16 or therapeutic agents which are therapeutically effective when (i) delivered at  
17 low transdermal fluxes and/or (ii) when present in low concentrations in the  
18 blood. Generally speaking, this aspect of the present invention is particularly  
19 applicable to the electrotransport delivery of highly potent drugs or other  
20 therapeutic agents.

21 The competitive ionic species can be loaded into the donor reservoir  
22 (e.g., a biocompatible salt is added to the donor reservoir) before  
23 electrotransport agent delivery and/or can be generated in situ during the  
24 operation of the electrotransport device. Generation of competitive ionic  
25 species in situ may be accomplished using a secondary electrode and  
26 appropriate electrical control circuitry as described in Phipps et al US Patent  
27 5,443,442 for example.

28 The amount of the competitive species intentionally added to the  
29 donor reservoir will be specific to the drug or agents to be delivered and the  
30 relative electrophoretic mobilities of the drug ions and the competing ionic  
31 species. Generally, the competitive species will be ionic and should have

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1 delivery characteristics similar to those of the drug being delivered. The  
2 quantity of co-delivered species to be added is selected so that the total  
3 current density is raised above the critical current density,  $I_c$ , where the ionic  
4 species efficiency is normalized or stabilized so that variation of delivery  
5 efficiency is no longer experienced.

6 The teachings in Theeuwes et al. U.S. Patent 5,080,646 may be  
7 utilized in determining the proper amount of competitive co-ion species to be  
8 added to the donor reservoir of an electrotransport delivery device. The  
9 patent discusses the processes involved in the transport of species through  
10 a biological surface such as skin, mucosa, or tissue. The Theeuwes et al  
11 patent provides a mathematical analysis which permits one skilled in this art,  
12 when unacceptable random variability of electrically-assisted drug flux is  
13 experienced, to select a suitable quantity and species of competitive co-ion  
14 to be delivered along with the drug or agent.

15 The transdermal electrotransport drug delivery efficiency may be  
16 increased, when using a pulsing electrotransport current, by maintaining the  
17 pulse width equal to or greater than  $t_c$ . In general, this requires the pulsing  
18 frequency to be maintained below about 100 Hz, and preferably less than  
19 about 10 Hz. The term "pulsing electrotransport current" as used herein  
20 means a current which varies in a periodic fashion. A pulsing  
21 electrotransport current which transforms the skin to the high efficiency  
22 transfer state is one where at least a portion of the periodic current  
23 waveform provides a current density below  $I_c$ , and another portion which has  
24 a sufficient magnitude and pulse width to effect transformation of the skin to  
25 the higher efficiency drug delivery state. This then provides the second of  
26 the two necessary and sufficient parameters (after current density  $I_c$ ) which  
27 must be satisfied to apply this invention. As was noted above, pulsing  
28 frequencies in the relatively low ranges discussed here combined with  
29 sufficient duty cycle, provide the pulse width needed for in vivo skin drug  
30 delivery efficiency to increase. For example, a frequency of about 10 Hz  
31 (i.e., a period of about 100 msec) and a duty cycle of 31% was found to

1 provide a pulse width of 31 msec which was long enough to induce a skin  
2 efficiency increase to deliver fentanyl at a current density of 0.1 mA/cm<sup>2</sup>.

3 Reference is now made to FIG. 3 which depicts an exemplary  
4 electrotransport device which can be used in accordance with the present  
5 invention. FIG. 3 shows a perspective exploded view of an electrotransport  
6 device 10 having an activation switch in the form of a push button switch 12  
7 and a display in the form of a light emitting diode (LED) 14. Device 10  
8 comprises an upper housing 16, a circuit board assembly 18, a lower  
9 housing 20, anode electrode 22, cathode electrode 24, anode reservoir 26,  
10 cathode reservoir 28 and skin-compatible adhesive 30. Upper housing 16  
11 has lateral wings 15 which assist in holding device 10 on a patient's skin.  
12 Upper housing 16 is preferably composed of an injection moldable elastomer  
13 (e.g., ethylene vinyl acetate). Printed circuit board assembly 18 comprises  
14 an integrated circuit 19 coupled to discrete electrical components 40 and  
15 battery 32. Circuit board assembly 18 is attached to housing 16 by posts  
16 (not shown in FIG. 3) passing through openings 13a and 13b, the ends of  
17 the posts being heated/melted in order to heat stake the circuit board  
18 assembly 18 to the housing 16. Lower housing 20 is attached to the upper  
19 housing 16 by means of adhesive 30, the upper surface 34 of adhesive 30  
20 being adhered to both lower housing 20 and upper housing 16 including the  
21 bottom surfaces of wings 15.

22 Shown (partially) on the underside of circuit board assembly 18 is a  
23 battery 32, which is preferably a button cell battery and most preferably a  
24 lithium cell. Other types of batteries, such as sizes AAA and AAAA, may  
25 also be employed to power device 10.

26 The circuit outputs (not shown in FIG. 3) of the circuit board assembly  
27 18 make electrical contact with the electrodes 24 and 22 through openings  
28 23,23' in the depressions 25,25' formed in lower housing, by means of  
29 electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn,  
30 are in direct mechanical and electrical contact with the top sides 44',44 of  
31 drug reservoirs 26 and 28. The bottom sides 46',46 of drug reservoirs 26,28

1 contact the patient's skin through the openings 29',29 in adhesive 30. Upon  
2 depression of push button switch 12, the electronic circuitry on circuit board  
3 assembly 18 delivers a predetermined DC current to the  
4 electrodes/reservoirs 22,26 and 24,28 for a delivery interval of predetermined  
5 length, e.g., about 10 minutes. Preferably, the device transmits to the user a  
6 visual and/or audible confirmation of the onset of the drug delivery, or bolus,  
7 interval by means of LED 14 becoming lit and/or an audible sound signal  
8 from, e.g., a "beeper". Drug (e.g., an analgesic drug such as fentanyl) is  
9 then delivered through the patient's skin, e.g., on the arm, for the  
10 predetermined (e.g., 10 minute) delivery interval. In practice, a user receives  
11 feedback as to the onset of the drug delivery interval by visual (LED 14  
12 becomes lit) and/or audible signals (a beep from the "beeper"). A preferred  
13 device is described in commonly owned, pending patent application entitled  
14 "Display for an Electrotransport Device", US Patent Application Serial  
15 Number 08/410,112, filed March 24, 1995.

16 Anodic electrode 22 is preferably comprised of silver and cathodic  
17 electrode 24 is preferably comprised of silver chloride. Both reservoirs 26  
18 and 28 are preferably comprised of polymer hydrogel materials as described  
19 herein. Electrodes 22, 24 and reservoirs 26, 28 are retained by lower  
20 housing 20. When the drug being delivered by electrotransport is cationic,  
21 the anodic reservoir 26 is the "donor" reservoir which contains the drug and  
22 the cathodic reservoir 28 contains a biocompatible electrolyte. When the  
23 drug being delivered by electrotransport is anionic, the cathodic reservoir 28  
24 is the "donor" reservoir which contains the drug and the anodic reservoir 26  
25 contains a biocompatible electrolyte.

26 The push button switch 12, the electronic circuitry on circuit board  
27 assembly 18 and the battery 32 are adhesively "sealed" between upper  
28 housing 16 and lower housing 20. Upper housing 16 is preferably  
29 composed of rubber or other elastomeric material. Lower housing 20 is  
30 preferably composed of a plastic or elastomeric sheet material (e.g.,  
31 polyethylene) which can be easily molded to form depressions 25,25' and cut

1 to form openings 23,23'. The assembled device 10 is preferably water  
2 resistant (i.e., splash proof) and is most preferably waterproof. The system  
3 has a low profile that easily conforms to the body thereby allowing freedom  
4 of movement at, and around, the wearing site. The anode/drug reservoir 26  
5 and the cathode/salt reservoir 28 are located on the skin-contacting side of  
6 device 10 and are sufficiently separated to prevent accidental electrical  
7 shorting during normal handling and use.

8 The device 10 adheres to the patient's body surface (e.g., skin) by  
9 means of a peripheral adhesive 30 which has upper side 34 and body-  
10 contacting side 36. The adhesive side 36 has adhesive properties which  
11 assures that the device 10 remains in place on the body during normal user  
12 activity, and yet permits reasonable removal after the predetermined (e.g.,  
13 24-hour) wear period. Upper adhesive side 34 adheres to lower housing 20  
14 and retains the electrodes and drug reservoirs within housing depressions  
15 25,25' as well as retains lower housing 20 attached to upper housing 16.

16 The push button switch 12 is located on the top side of device 10 and  
17 is easily actuated through clothing. A double press of the push button  
18 switch 12 within a short period of time, e.g., three seconds, is preferably  
19 used to activate the device 10 for delivery of drug, thereby minimizing the  
20 likelihood of inadvertent actuation of the device 10.

21 Upon switch activation an audible alarm signals the start of drug  
22 delivery, at which time the circuit supplies a predetermined level of DC  
23 current to the electrodes/reservoirs for a predetermined (e.g., 10 minute)  
24 delivery interval. The LED 14 remains "on" throughout the delivery interval  
25 indicating that the device 10 is in an active drug delivery mode. The battery  
26 preferably has sufficient capacity to continuously power the device 10 at the  
27 predetermined level of DC current for the entire (e.g., 24 hour) wearing  
28 period.

29 The present invention is particularly useful in the transformation of  
30 human skin in the transdermal electrotransport delivery of drugs to humans.

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The terms "agent" and "drug" are used interchangeably herein and are intended to have their broadest interpretation as any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics and analgesic combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, anti-motion sickness preparations, anti-nauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics including gastrointestinal and urinary antispasmodics, anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, beta-blockers, antiarrhythmics, antihypertensives, diuretics, vasodilators including general, coronary, peripheral and cerebral vasodilators, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, proteins, peptides, polypeptides and other macromolecules, psychostimulants, sedatives and tranquilizers.

23 The present invention can be used to deliver transdermally by  
24 electrotransport the following drugs: interferons, alfentanil, amphotericin B,  
25 angiopeptin, baclofen, beclomethasone, betamethasone, bisphosphonates,  
26 bromocriptine, buserelin, buspirone, calcitonin, ciclopirox, olamine, copper,  
27 cromolyn sodium, desmopressin, diclofenac diflorasone, diltiazem,  
28 dobutamine, dopamine agonists, dopamine agonists, doxazosin, droperidol,  
29 enalapril, enalaprilat, fentanyl, encainide, G-CSF, GM-CSF, M-CSF, GHRF,  
30 GHRH, gonadorelin, goserelin, granisetron, haloperidol, hydrocortisone,  
31 indomethacin, insulin, insulinotropin, interleukins, isosorbide dinitrate.

1 ketoprofen, ketorolac, leuprolide, LHRH, lidocaine, lisinopril, LMW heparin,  
2 melatonin, methotrexate, metoclopramide, miconazole, midazolam, nafarelin,  
3 nicardipine, NMDA antagonists, octreotide, ondansetron, oxybutynin, PGE<sub>1</sub>,  
4 piroxicam, pramipexole, prazosin, prednisolone, prostaglandins, scopolamine,  
5 seglitide, sufentanil, terbutaline, testosterone, tetracaine, tropisetron,  
6 vapreotide, vasopressin, verapamil, warfarin, zacopride, zinc, and zotasetron.

7 This invention is also believed to be useful in the transdermal  
8 electrotransport delivery of peptides, polypeptides and other macromolecules  
9 typically having a molecular weight of at least about 300 daltons, and  
10 typically a molecular weight in the range of about 300 to 40,000 daltons.  
11 Specific examples of peptides and proteins in this size range include, without  
12 limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, nafarelin  
13 and leuprolide, GHRH, insulin, heparin, calcitonin, endorphin, TRH, NT-36  
14 (chemical name: N=[[(s)-4-oxo-2-azetidiny]carbonyl]-L-histidyl-L-  
15 prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG,  
16 desmopressin acetate, etc.), follicle luteoids,  $\alpha$ ANF, growth hormone  
17 releasing factor (GHRF),  $\beta$ MSH, TGF- $\beta$ , somatostatin, atrial natriuretic  
18 peptide, bradykinin, somatotropin, platelet-derived growth factor,  
19 asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic  
20 gonadotropin, corticotropin (ACTH), epidermal growth factor, erythropoietin,  
21 epoprostenol (platelet aggregation inhibitor), follicle stimulating hormone,  
22 glucagon, hirulogs, hyaluronidase, interferons, insulin-like growth factors,  
23 interleukins, menotropins (urofollitropin (FSH) and LH), oxytocin,  
24 streptokinase, tissue plasminogen activator, urokinase, vasopressin, ACTH  
25 analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists,  
26 antidiuretic hormone agonists, antidiuretic hormone antagonists, bradykinin  
27 antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE  
28 peptide suppressors, IGF-1, neuropeptide Y, neurotrophic factors, opiate  
29 peptides, parathyroid hormone and agonists, parathyroid hormone  
30 antagonists, prostaglandin antagonists, pentigetide, protein C, protein S,

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1 ramoplanin, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines,  
2 vasopressin antagonist analogs, alpha-1 anti-trypsin (recombinant).

3 Generally speaking, it is most preferable to use a water soluble form  
4 of the drug or agent to be delivered. Drug or agent precursors, i.e., species  
5 which generate the selected species by physical or chemical processes such  
6 as ionization, dissociation, dissolution or covalent chemical modification (i.e.,  
7 prodrugs), are within the definition of "agent" or "drug" herein. "Drug" or  
8 "agent" is to be understood to include charged and uncharged species as  
9 described above.

10 While the disclosure has focussed upon the electrotransport delivery  
11 of ionic species, the present invention is also applicable to the  
12 electrotransport delivery of uncharged species, e.g., by electroosmosis.  
13 Thus, the transformation of the skin into the high efficiency transport state is  
14 not limited to electrically assisted transport of ionic species but also to  
15 electroosmotic delivery of uncharged (i.e., non-ionized) species.

16 The following examples illustrate some of the advantages of the  
17 present invention.

18

#### 19 EXAMPLE 1

##### 20 Current Density and Increased Efficiency

21 This study evaluated the effect of applied current on electrotransport  
22 drug delivery efficiency. Drug delivery efficiency is expressed in terms of the  
23 rate of drug delivery per unit of applied current. The study involved the  
24 application of electrotransport devices to eighteen healthy male volunteers  
25 for a duration of about one day.

26 The two electrotransport treatments involved the delivery of fentanyl  
27 from a donor reservoir containing an aqueous solution of fentanyl HCl and  
28 having a skin contact area of 5 cm<sup>2</sup>, at a baseline current of 100  $\mu$ A. Thus,  
29 the applied electrotransport current density was 20  $\mu$ A/cm<sup>2</sup> (= 100  $\mu$ A  $\div$  5  
30 cm<sup>2</sup>). Six of the eighteen volunteers were administered 4 bolus doses during  
31 the first hour of treatment by applying current levels of 1300  $\mu$ A (i.e., an

1 applied electrotransport current density of  $260 \mu\text{A}/\text{cm}^2$ ) for a duration of 2.5  
2 minutes at 15 minute intervals. Following the administration of the four  
3 boluses in the first hour of treatment, these six volunteers received  
4 continuous transdermal electrotransport fentanyl administration at a current  
5 density of  $20 \mu\text{A}/\text{cm}^2$  from hour 2 through 24 hours. The remaining twelve  
6 volunteers received continuous transdermal electrotransport fentanyl  
7 administration at a current density of  $20 \mu\text{A}/\text{cm}^2$  over the entire 24 hour  
8 delivery period. After the treatment period, the electrotransport devices were  
9 removed. The skin site was then washed to remove any residual fentanyl.

10 Blood samples were taken over the entire 24 hour period commencing  
11 with the application of current from the electrotransport devices. Serum  
12 fentanyl concentrations were used to calculate mean transdermal fentanyl  
13 fluxes using subject specific pharmacokinetic parameters and conventional  
14 methods.

15 FIG. 5 shows that once a skin site receives a minimum level of  
16 current (for a fixed electrode area) for a sufficient duration, a high  
17 electrotransport efficiency state is achieved. FIG. 5 shows the mean serum  
18 fentanyl concentration in the blood of the subjects over the 24 hour testing  
19 period. As is shown in the uppermost curve ( $\diamond \cdots \diamond \cdots \diamond$ ) in FIG. 5, the six  
20 volunteers which received the four  $260 \mu\text{A}/\text{cm}^2$ , 2.5 minute bolus  
21 administrations in the first hour exhibited higher efficiency fentanyl  
22 transdermal delivery than the group of twelve subjects shown as three  
23 groups of four in the three lower curves (to emphasize inherent variability)  
24 who received only the  $20 \mu\text{A}/\text{cm}^2$  constant DC current. Once this high-  
25 efficiency transport state is achieved, more drug is delivered through the skin  
26 per unit of applied current. Further, the effect lasted the entire 24 hours of  
27 the treatment. This is indicated by the vertical separation between the upper  
28 curve and the three lower curves in FIG. 5.

29 Specifically, the six volunteers who received the four  $260 \mu\text{A}/\text{cm}^2$   
30 doses in the first hour of treatment exhibited a mean transdermal fentanyl  
31 flux of  $113 \mu\text{g}/\text{h}$  while the twelve volunteers who received only the  $20 \mu\text{A}/\text{cm}^2$

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1 baseline current exhibited a mean transdermal fentanyl flux of 57  $\mu\text{g/h}$ . This  
2 indicates that the efficiency was enhanced by about a factor of two as a  
3 result of the initial high current density boluses.

4

5 EXAMPLE 2

6 Current Density and Fentanyl Flux

7 This study was undertaken to evaluate the relationship of current  
8 density and drug flux in the transdermal electrotransport delivery of fentanyl.  
9 Electrotransport devices, delivering constant DC currents, were applied to 8  
10 healthy male volunteers for a duration of 24 hours. The three  
11 electrotransport treatment regimens in this study differed only in the applied  
12 electrotransport current (and therefore current density) levels. The  
13 electrotransport devices delivered fentanyl through the skin from a donor  
14 hydrogel having a skin contact surface area of 5  $\text{cm}^2$ . The gels were  
15 imbibed with an aqueous solution of fentanyl HCl. The current density levels  
16 used in this study were 10, 20, and 40  $\mu\text{A}/\text{cm}^2$ . After a 24 hour treatment  
17 period, the electrotransport devices were removed. The skin site was then  
18 washed to remove any residual fentanyl. All 8 volunteers received each  
19 treatment approximately 1 week apart.

20 For each treatment, blood samples were taken over a 24 hour period  
21 commencing with the application of current from the electrotransport devices.  
22 Serum fentanyl concentrations over the first 24 hours are shown in FIG. 6.  
23 The top curve ( $-\Delta-\Delta-\Delta-$ ) in FIG. 6 was the 200  $\mu\text{A}$  treatment (i.e., 40  
24  $\mu\text{A}/\text{cm}^2$ ), the middle curve ( $-\square-\square-\square-$ ) the 100  $\mu\text{A}$  treatment (i.e., 20  $\mu\text{A}/\text{cm}^2$ )  
25 and the bottom curve ( $-O-O-O-$ ) the 50  $\mu\text{A}$  treatment (i.e., 10  $\mu\text{A}/\text{cm}^2$ ). As  
26 in Example 1, the serum fentanyl concentrations from each patient were  
27 used to calculate mean drug rate and the mean total amount of drug  
28 delivered. A drug delivery efficiency level for each treatment was derived by  
29 dividing the mean fentanyl rate by the current density applied to the skin.

30 The average transdermal fentanyl rates were 19, 73 and 173  $\mu\text{g/h}$  at  
31 the applied current densities 10, 20 and 40  $\mu\text{A}/\text{cm}^2$ , respectively. This data

1 shows a non-linear relationship between applied current and transdermal  
2 electrotransport drug flux within the electrotransport current density range of  
3 10 to 40  $\mu\text{A}/\text{cm}^2$ . An almost ten-fold increase in drug rate was observed as  
4 the current was increased four-fold from 50 $\mu\text{A}$  to 200  $\mu\text{A}$ . This unexpected  
5 result indicates that the efficiency of fentanyl delivery was enhanced by a  
6 factor of about 2.5-fold due to the change in current density from 10 to 40  
7  $\mu\text{A}/\text{cm}^2$ .

8

9

### EXAMPLE 3

10 This study was undertaken to evaluate the relationship between  
11 current density and drug flux in the transdermal electrotransport delivery of  
12 goserelin. The study involved the application of electrotransport devices,  
13 applying constant current, to 12 normal male volunteers for a duration of 8  
14 hours.

15 The two electrotransport treatment regimens in this study differed only  
16 in applied current density levels. The electrotransport devices delivered  
17 goserelin through the skin from polyvinyl alcohol (PVOH)-based donor  
18 hydrogels having a skin-contact surface area of 4  $\text{cm}^2$ . The gels contained  
19 an aqueous goserelin solution. The current density levels used in this study  
20 were 50 and 100  $\mu\text{A}/\text{cm}^2$ . After an 8 hour treatment period, the  
21 electrotransport devices were removed. The skin site was then washed to  
22 remove any residual goserelin. All 12 volunteers received each treatment  
23 seven days apart.

24 For each treatment, seven blood samples were taken over a 24 hour  
25 period commencing with the application of current from the electrotransport  
26 devices. Serum goserelin concentrations from each patient were used to  
27 calculate mean drug flux and the mean total amount of drug delivered.

28 FIG. 8 shows the goserelin blood plasma concentrations for the 8  
29 hour duration of electrotransport administration for the two current densities  
30 (i.e., 50 and 100  $\mu\text{A}/\text{cm}^2$ ). The 100  $\mu\text{A}/\text{cm}^2$  curve is the upper curve in FIG.  
31 8 while the lower curve in FIG. 8 is the 50  $\mu\text{A}/\text{cm}^2$  data. From this

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1 concentration data, transdermal goserelin fluxes were calculated. The  
2 average transdermal goserelin flux was 5.8  $\mu\text{g/h}$  at an applied current  
3 density of 50  $\mu\text{A/cm}^2$  while the average transdermal flux of goserelin was  
4 21.6  $\mu\text{g/h}$  at an applied current density of 100  $\mu\text{A/cm}^2$ . Thus, a non-linear  
5 relationship between applied current density and drug flux was shown by the  
6 data. An almost four-fold increase in drug flux is observed as the current  
7 density rises from 50 to 100  $\mu\text{A/cm}^2$ . This data also suggests the existence  
8 of a critical current density,  $I_c$ , which for transdermal electrotransport delivery  
9 of goserelin falls between 50 and 100  $\mu\text{A/cm}^2$ , above which more drug is  
10 delivered through the skin per unit of applied current.

11 The remaining example utilizes a pulsing electrotransport  
12 current, and is therefore relevant only to a preferred aspect of the present  
13 invention wherein the applied electrotransport current is a pulsing current  
14 with current pulses having a pulse width of at least 5 msec, and more  
15 preferably a pulse width of at least 10 msec.

16

#### 17 EXAMPLE 4

##### 18 Pulsing Frequency and Fentanyl Flux

19 This study assessed the effect of pulsing frequency on the  
20 electrotransport delivery of fentanyl using pulsed current waveforms. The  
21 frequencies evaluated in this study were 1, 10, and 625 Hz.

22 The electrotransport devices were configured to deliver a 200  $\mu\text{A}$   
23 square wave current pulse, having a 31% duty cycle. The electrotransport  
24 devices delivered fentanyl through the skin from a donor hydrogel having a  
25 skin contact surface area of 2  $\text{cm}^2$ . Thus, during the applied electrotransport  
26 current pulses, the current density was 100  $\mu\text{A/cm}^2$  ( $= 200 \mu\text{A} \div 2 \text{ cm}^2$ ). The  
27 gels were imbibed with an aqueous solution of fentanyl HCl. After treatment  
28 periods of varying duration, the electrotransport devices were removed. The  
29 skin site was then washed to remove any residual fentanyl.

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1 For each treatment, blood samples were taken commencing with the  
2 application of current from the electrotransport devices. Serum fentanyl  
3 levels from each patient were used to calculate mean drug flux.

4 FIG. 7 shows that the use of a square-wave frequency of 625 Hz  
5 resulted in minimal fentanyl flux. This is shown in the lower most nearly  
6 horizontal curve in FIG. 7. The use of the lower pulsing frequencies, 1 and  
7 10 Hz, resulted in increased fentanyl flux. This is shown in the upper two  
8 curves of FIG. 7. No statistically significant difference in fentanyl flux was  
9 observed between 1 and 10 Hz. These results suggest that the use of lower  
10 pulsing frequencies results in higher electrotransport delivery efficiency of  
11 fentanyl.

12 The above disclosure will suggest many alternatives, permutations,  
13 and variations of the invention to one skilled in this art without departing from  
14 the scope of the invention. The above disclosure is intended to be  
15 illustrative and not exhaustive. All such, permutations, variations, and  
16 alternatives suggested by the above disclosure are to be included within the  
17 scope of the attached claims.

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1 We Claim:

2  
3 1. An electrotransport device for in vivo delivery of a charged agent  
4 through a body surface at a higher electrotransport agent delivery efficiency (E)  
5 defined by the agent delivery rate per unit of applied current; the device (10) having  
6 a donor reservoir (26, 46) containing the charged agent and having a delivery area,  
7 and having a source of electrical power (32) and a current controller (19, 40), the  
8 device (10) being characterized by:

9 the current controller (19, 40) being adapted to provide an applied pulsing  
10 current having a periodic current waveform, a pulsing frequency, and a duty cycle,  
11 the pulsing current applied to the reservoir (26, 46) and to the body surface, wherein  
12 an applied current density is defined by the applied pulsing current divided by the  
13 delivery area, and wherein the body surface exhibits a higher electrotransport agent  
14 delivery efficiency (E) when the applied current density is greater than or equal to a  
15 critical current density level ( $I_c$ ) and the applied pulsing current is applied for greater  
16 than or equal to a critical time period ( $t_c$ ).  
17

18 2. The device of claim 1, wherein the agent delivery efficiency (E) is more  
19 stable when the applied current density is above the critical level ( $I_c$ ) and less stable  
20 when the applied current density is below the critical level ( $I_c$ ).  
21

22 3. The device of claim 1, wherein the device (10) is adapted to be applied  
23 to intact human skin and the controller (19, 40) is adapted to provide an applied  
24 current density of at least about  $40 \mu\text{A}/\text{cm}^2$ .  
25

26 4. The device of claim 1, wherein the agent is fentanyl and the controller  
27 (19, 40) is adapted to provide an applied current density of at least about  $40 \mu\text{A}/\text{cm}^2$   
28 for at least about 10 msec.  
29

1           5.     The device of claim 1, wherein the agent is goserelin and the controller  
2 (19, 40) is adapted to vary and control the periodic current waveform to provide an  
3 applied current density of at least about  $50 \mu\text{A}/\text{cm}^2$  for at least about 10 msec.  
4

5           6.     The device of claim 1, wherein  $t_c$  is at least 5 msec.  
6

7           7.     The device of claim 1, wherein the periodic current waveform has a  
8 current magnitude that provides a second applied current density less than  $I_c$ .  
9

10          8.     The device of claim 7, wherein the second applied current density is  
11 approximately zero.  
12

13          9.     The device of claim 7, wherein the controller (19, 40) is adapted to  
14 vary the duty cycle and the agent delivery rate.  
15

16          10.    The device of claim 7, wherein the controller (19, 40) is adapted to  
17 vary the frequency and the agent delivery rate.  
18

19          11.    The device of claim 1, wherein the donor reservoir contains at least  
20 one suitable competitive specie.  
21

22          12.    The device of claim 1, wherein the controller (19, 40) is adapted to  
23 vary and control the frequency of the applied pulsing current to less than about 100  
24 Hz.  
25

26          13.    The device of claim 1, wherein the controller (19, 40) is adapted to  
27 vary and control the frequency of the applied pulsing current to less than about 10  
28 Hz.

1           14.    A method of in vivo delivery of a charged agent from an  
2 electrotransport delivery device (10) through a body surface at higher  
3 electrotransport agent delivery efficiency (E) defined by the agent delivery rate per  
4 unit of applied current; the device (10) having a donor reservoir (26, 46) containing  
5 the agent and having a delivery area, and having a source of electrical power (32)  
6 and a current controller (19, 40), the method being characterized by the steps of:  
7           adapting the current controller (19, 40) to provide an applied pulsing current  
8 having a periodic current waveform, a pulsing frequency, and a duty cycle, the  
9 pulsing current applied to the reservoir (26, 46) and to the body surface, wherein an  
10 applied current density is defined by the applied pulsing current divided by the  
11 delivery area, and wherein the body surface exhibits a higher electrotransport agent  
12 delivery efficiency (E) when the applied current density is greater than or equal to a  
13 critical current density level ( $I_c$ ) and the applied pulsing current is applied for greater  
14 than or equal to a critical time period ( $t_c$ ).  
15

16           15.    The method of claim 14, wherein the agent delivery efficiency (E) is  
17 more stable at a current density above the critical level ( $I_c$ ) and less stable at a  
18 current density below the critical level ( $I_c$ ).  
19

20           16.    The method of claim 14, wherein the device is adapted to be applied to  
21 human skin, and the controller (19, 40) provides an applied current density at least  
22 about  $40 \mu\text{A}/\text{cm}^2$ .  
23

24           17.    The method of claim 14, wherein the agent is fentanyl, and the  
25 controller (19, 40) provides an applied current density of at least  $40 \mu\text{A}/\text{cm}^2$  for at  
26 least about 10 msec.  
27

28           18.    The method of claim 14, wherein the pulsing frequency is less than  
29 about 100 Hz.  
30

AMENDED SHEET

1           19.    The method of claim 14, wherein the pulsing frequency less than about  
2   10 Hz.

3  
4           20.    The method of claim 14, wherein the duty cycle is less than about  
5   100%.

6  
7           21.    The method of claim 14, wherein the body surface comprises intact  
8   human skin and  $I_c$  is at least about  $40 \mu\text{A}/\text{cm}^2$ .

9  
10          22.    The method of claim 14, wherein the agent is fentanyl, the body  
11   surface is intact human skin, and the applied pulsing current is equal to  $I_c$  which is at  
12   least about  $40 \mu\text{A}/\text{cm}^2$ , and wherein the pulsing current is applied for at least about  
13   10 msec.

14  
15          23.    The method of claim 14, wherein the agent is goserelin, and the  
16   applied pulsing current is at least about  $50 \mu\text{A}/\text{cm}^2$ , and wherein the pulsing current  
17   is applied for at least about 10 msec.

18  
19          24.    The method of claim 14 further including the step of varying the duty  
20   cycle and the agent delivery rate.

21  
22          25.    The method of claim 14 further including the step of varying the  
23   pulsing frequency and the agent delivery rate.

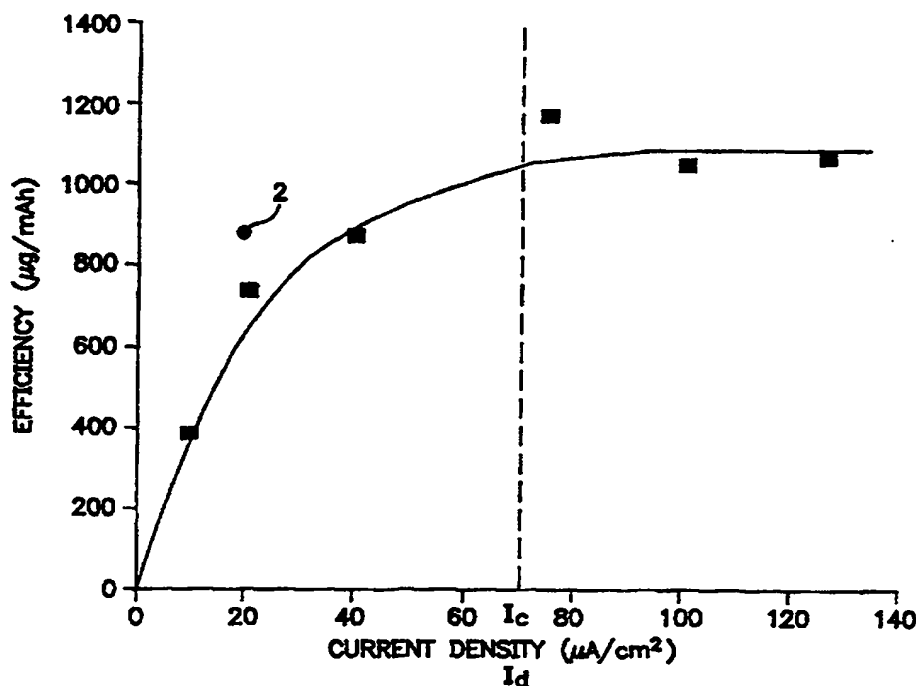
24  
25          26.    The method of claim 14 further including the step of adding a suitable  
26   competitive specie to the donor reservoir (26, 46).



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US96/09989 (22) International Filing Date: 7 June 1996 (07.06.96) (30) Priority Data: 08/483,069                      7 June 1995 (07.06.95)                      US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): PHIPPS, J., Bradley [US/US]; 5309 Ximines Lane, Plymouth, MN 55442 (US). LATTIN, Gary, A. [US/US]; 6927 145th Avenue, Forest Lake, MN 55025 (US). HAAK, Ronald, P. [US/US]; 2647 Alpine Road, Menlo Park, CA 94025 (US). THEEUWES, Felix [BE/US]; 27350 Altamont Road, Los Altos Hills, CA 94022 (US). GUPTA, Suneel [IN/US]; 4028 Farm Hill Road, No. 5, Redwood City, CA 94061 (US). (74) Agents: MILLER, D., Byron et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS



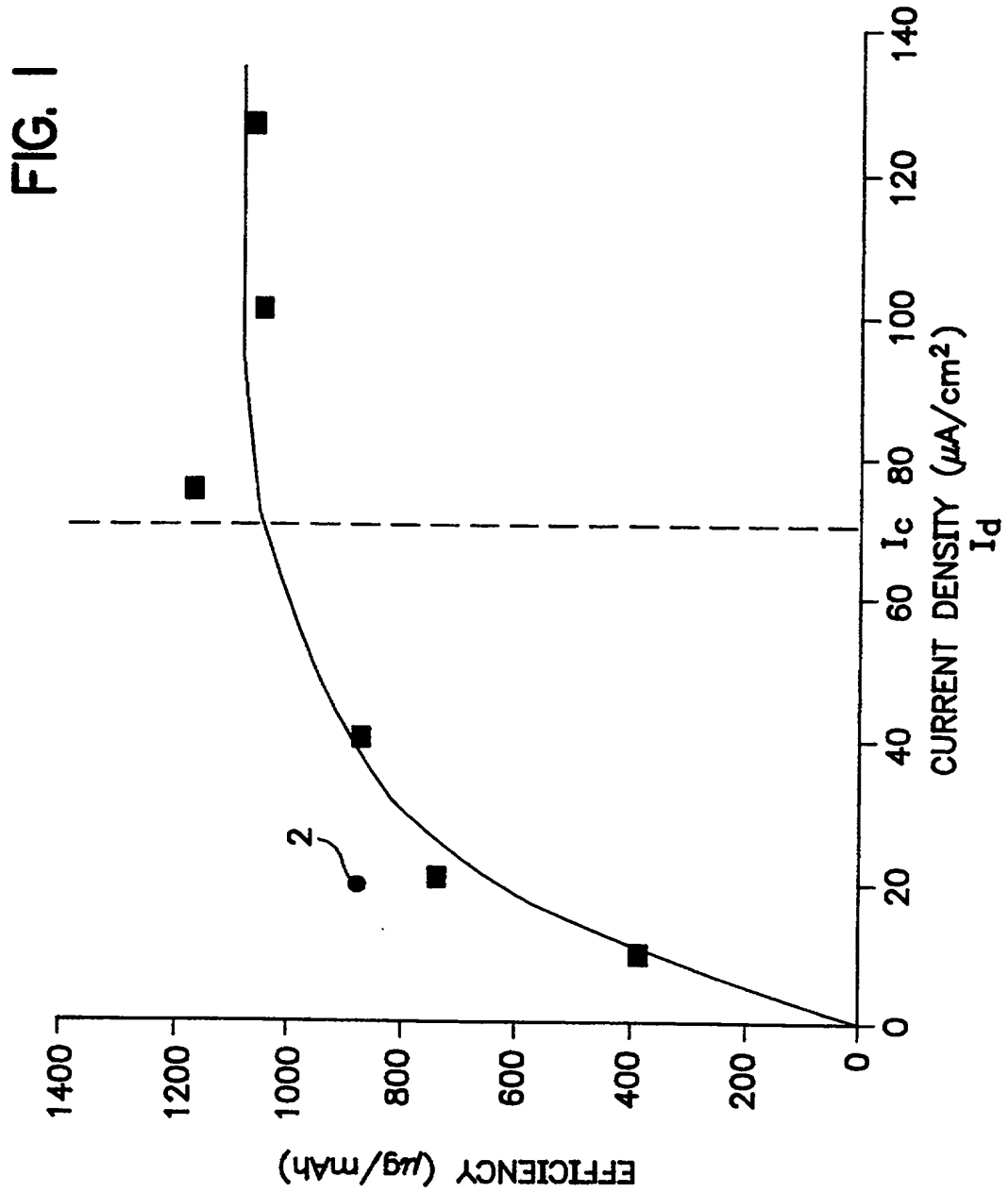
## (57) Abstract

An electrotransport agent delivery device (10) for delivering a therapeutic agent through intact skin, and a method of operating same, is provided. The device applies a pulsing electrotransport current wherein current pulses have a magnitude above a critical level ( $I_c$ ) at which the skin is transformed into a higher electrotransport delivery efficiency (E) state. Most preferably the length of the applied current pulses is at least 5 msec and preferably at least 10 msec.

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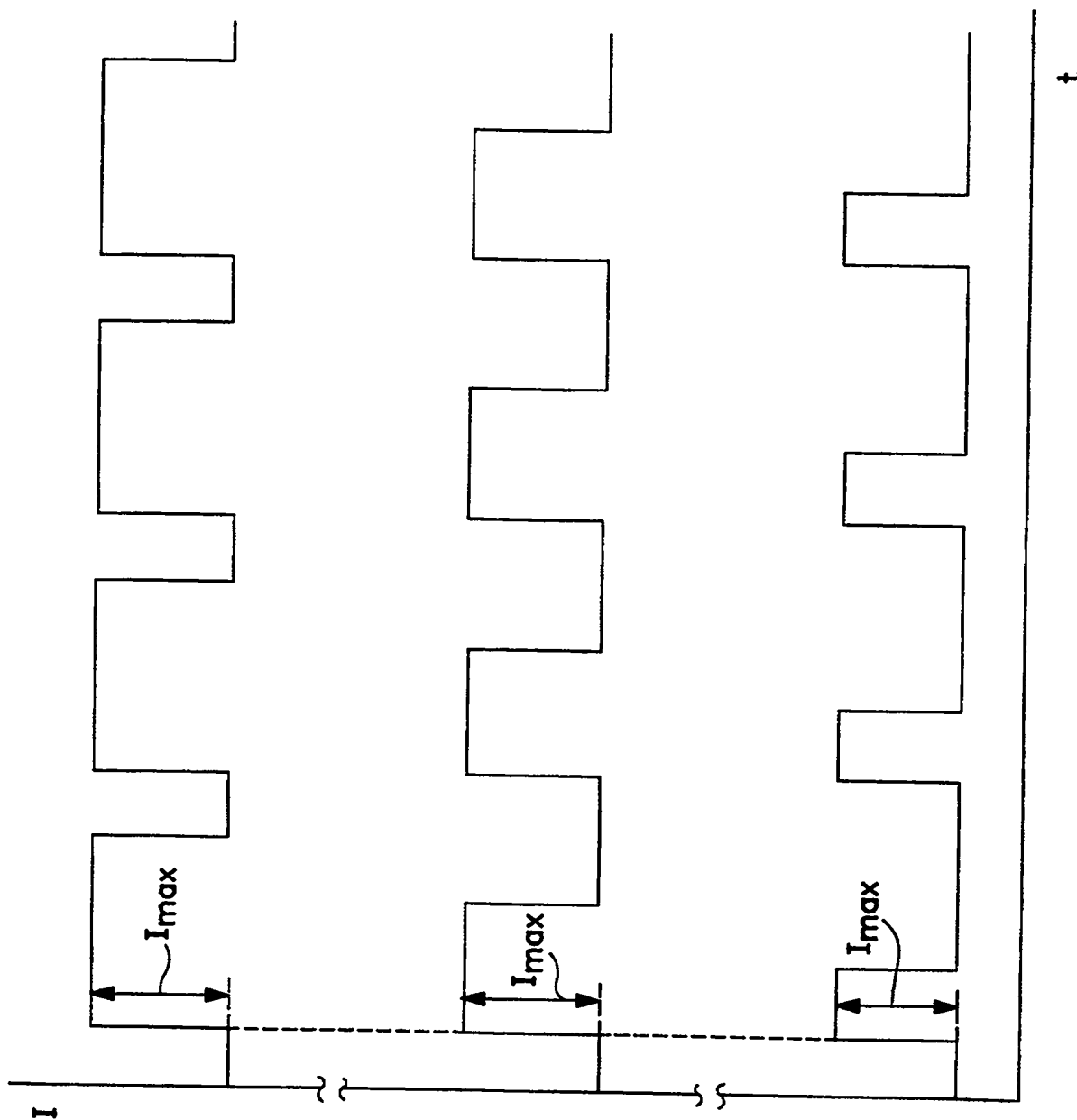
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APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN	WO	96/40364

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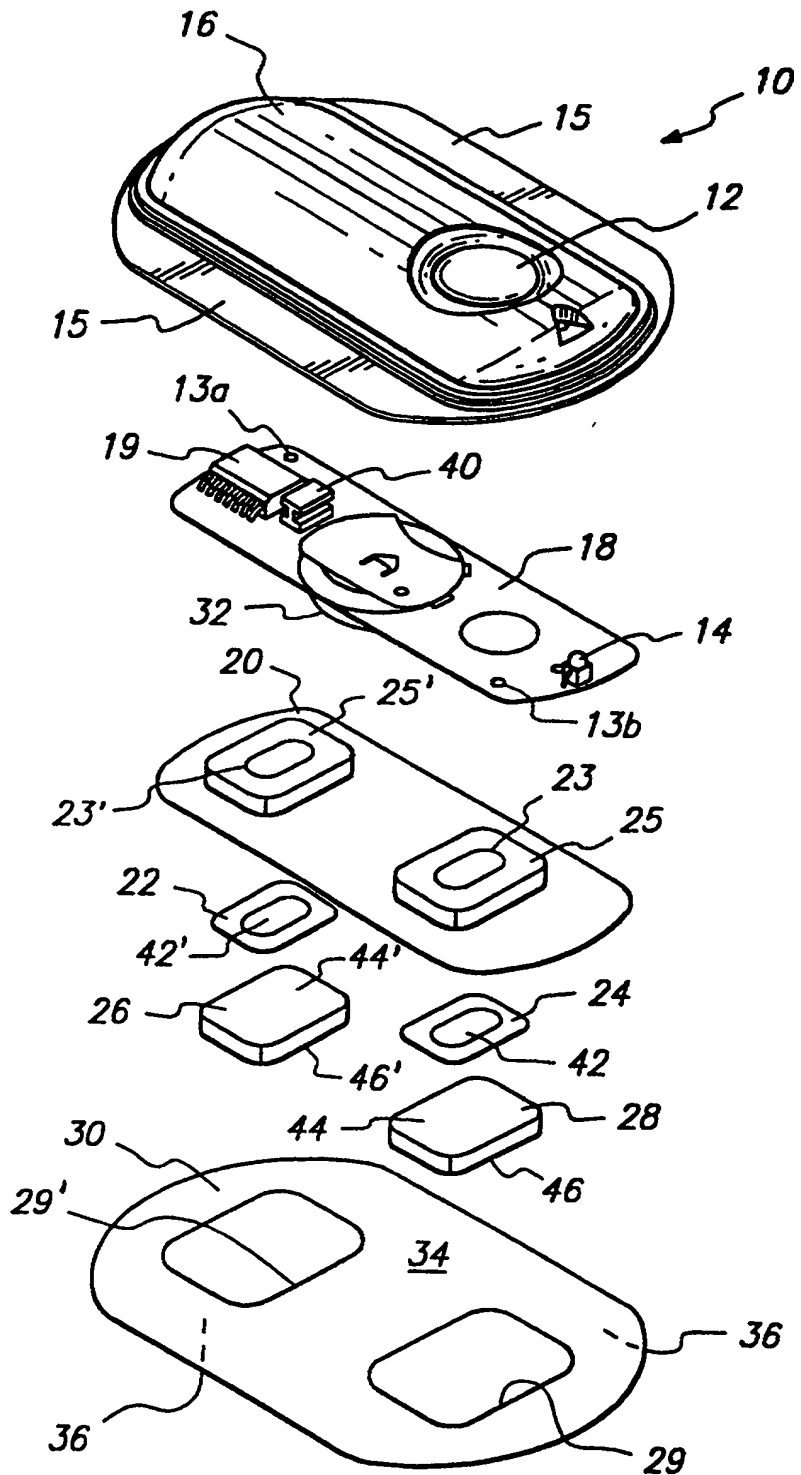
FIG. 2



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FIG. 3

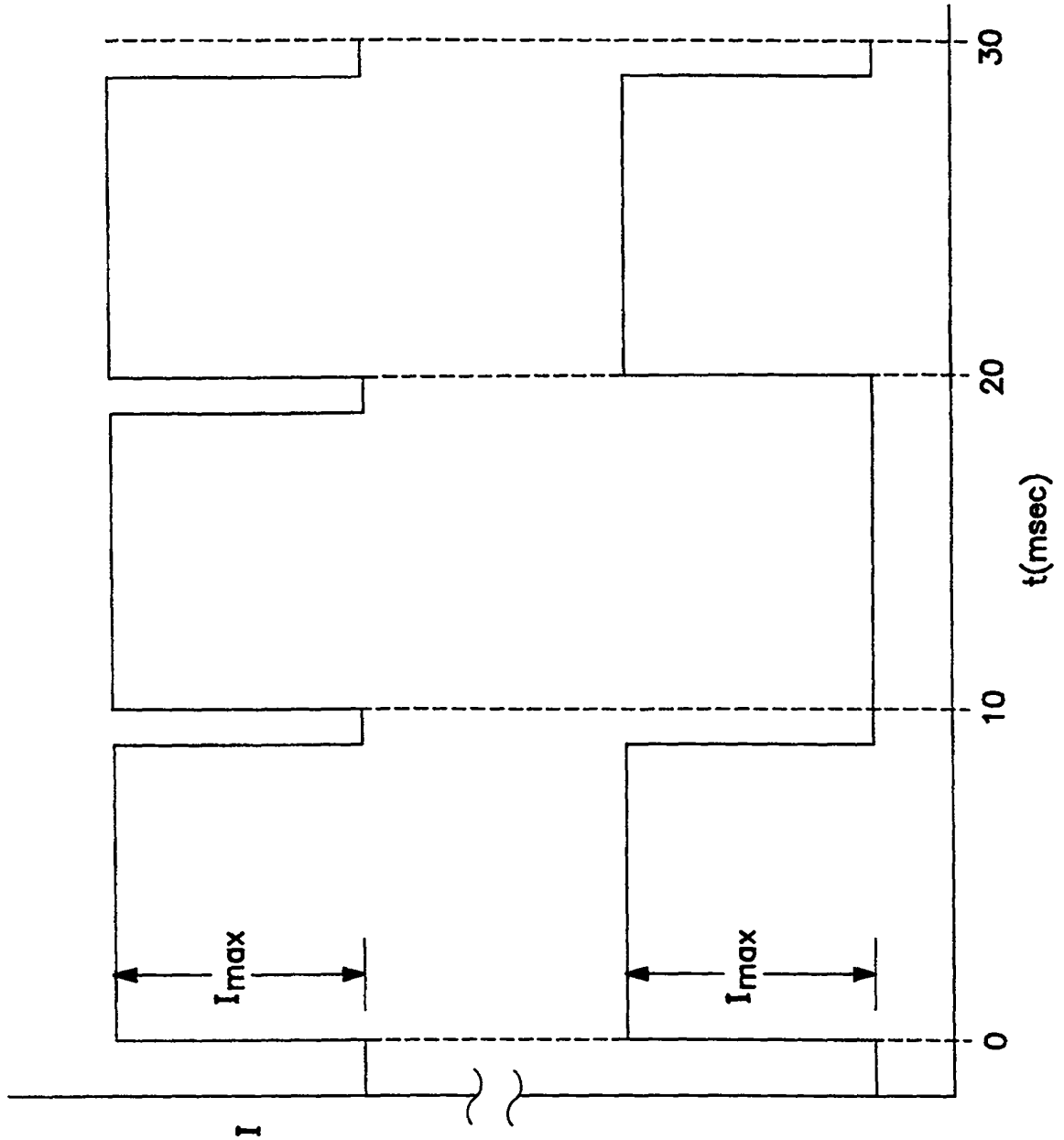


APPROVED	O.G. FIG.	
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FIG. 4



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FIG. 5

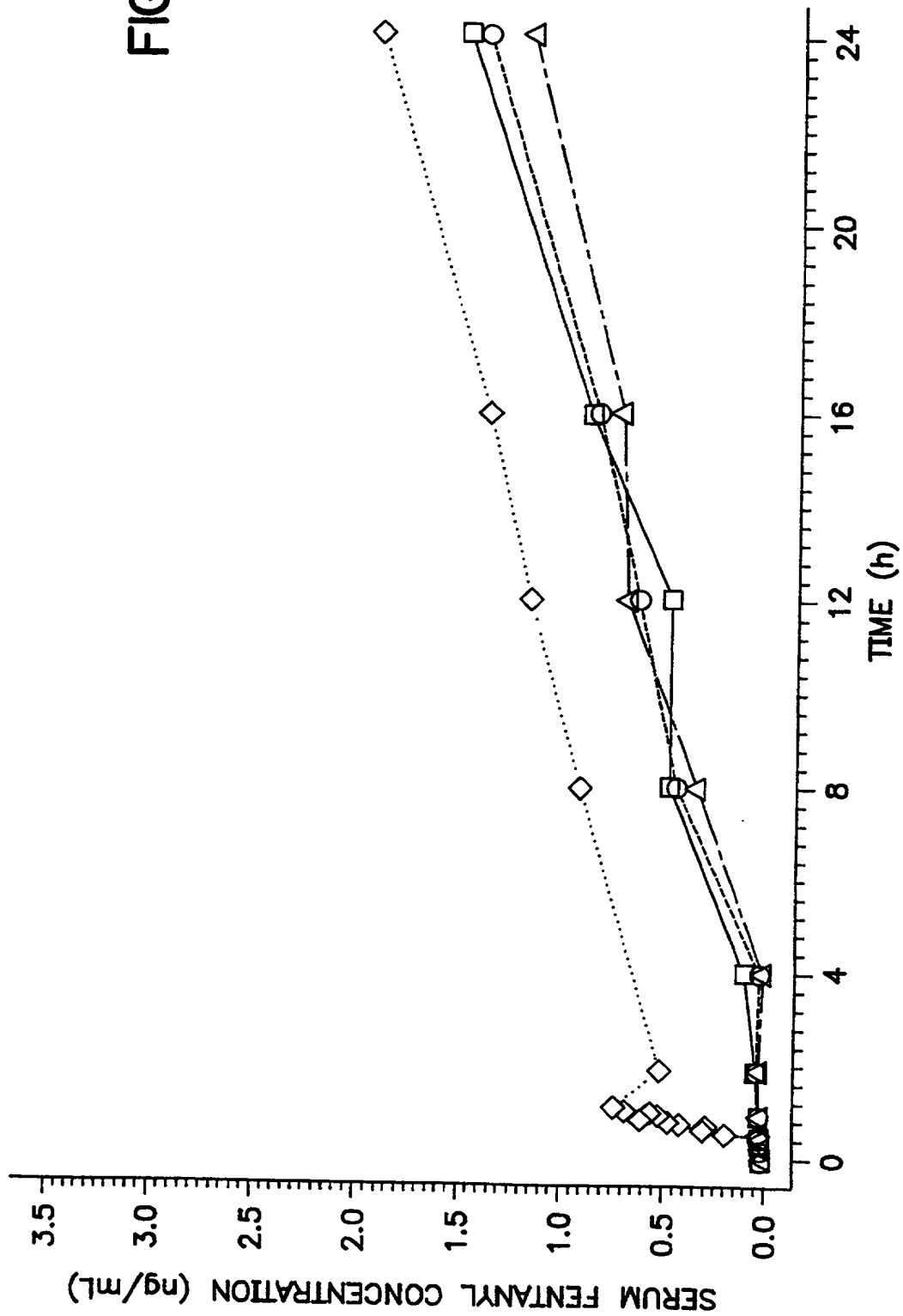
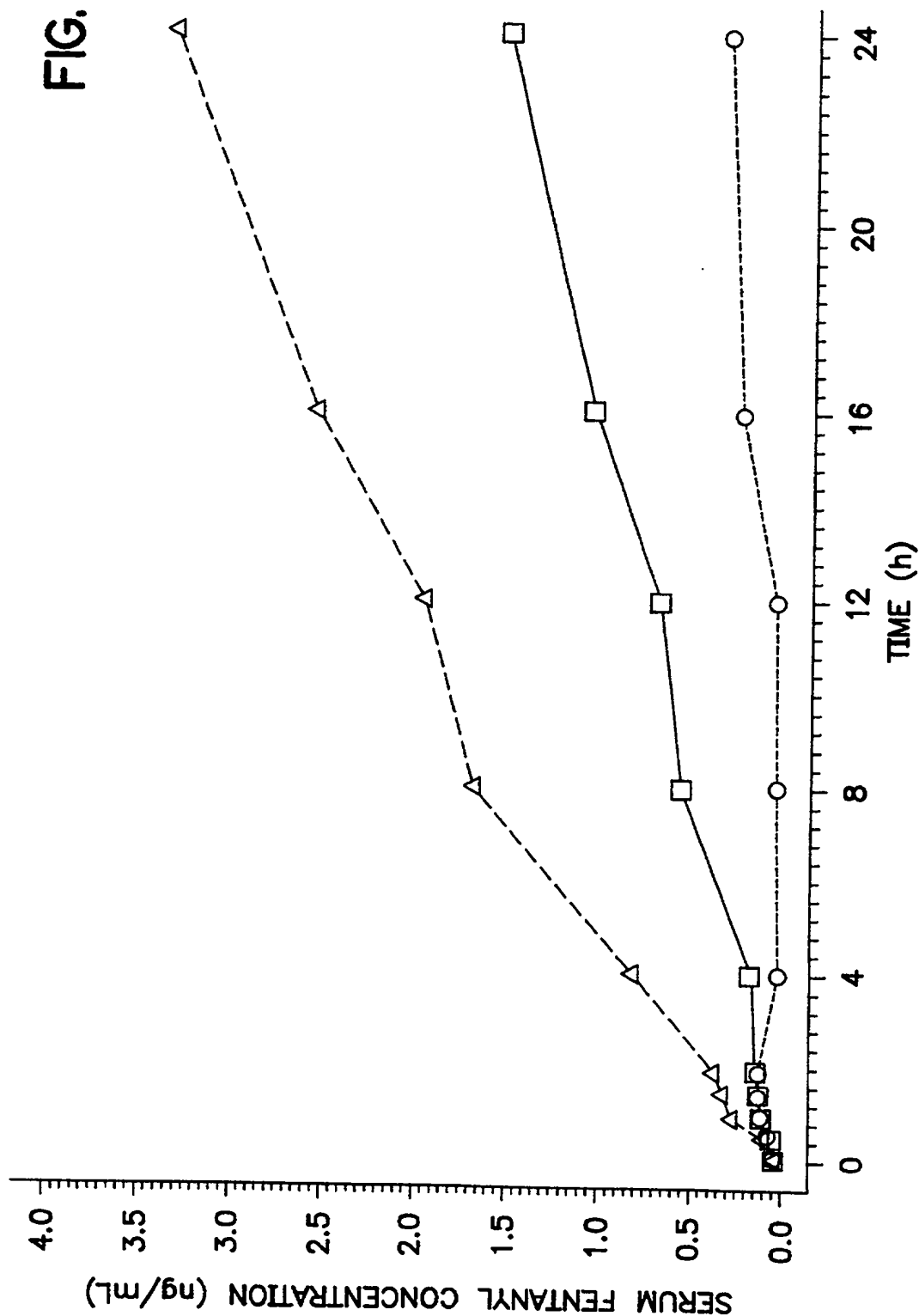
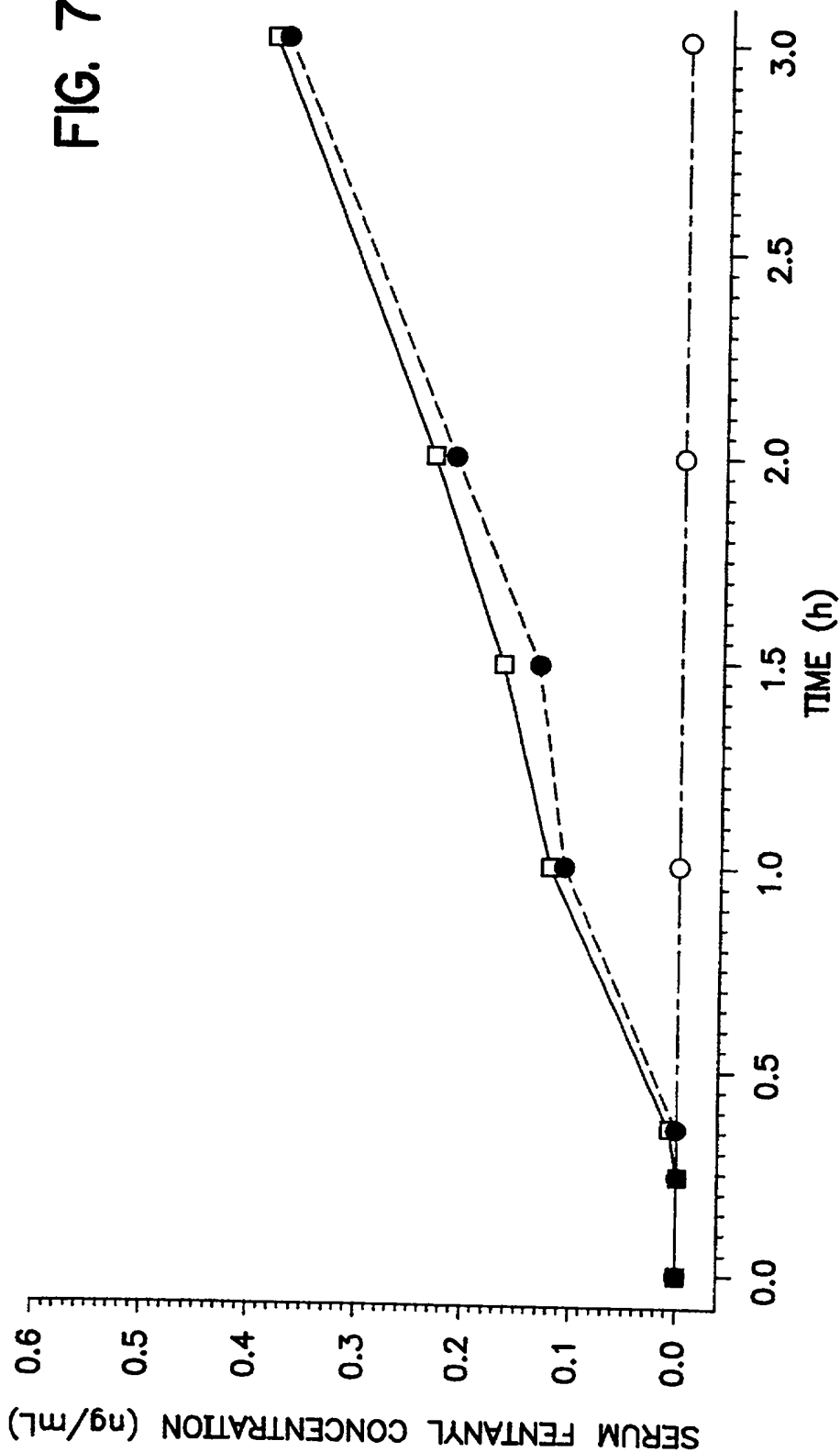


FIG. 6



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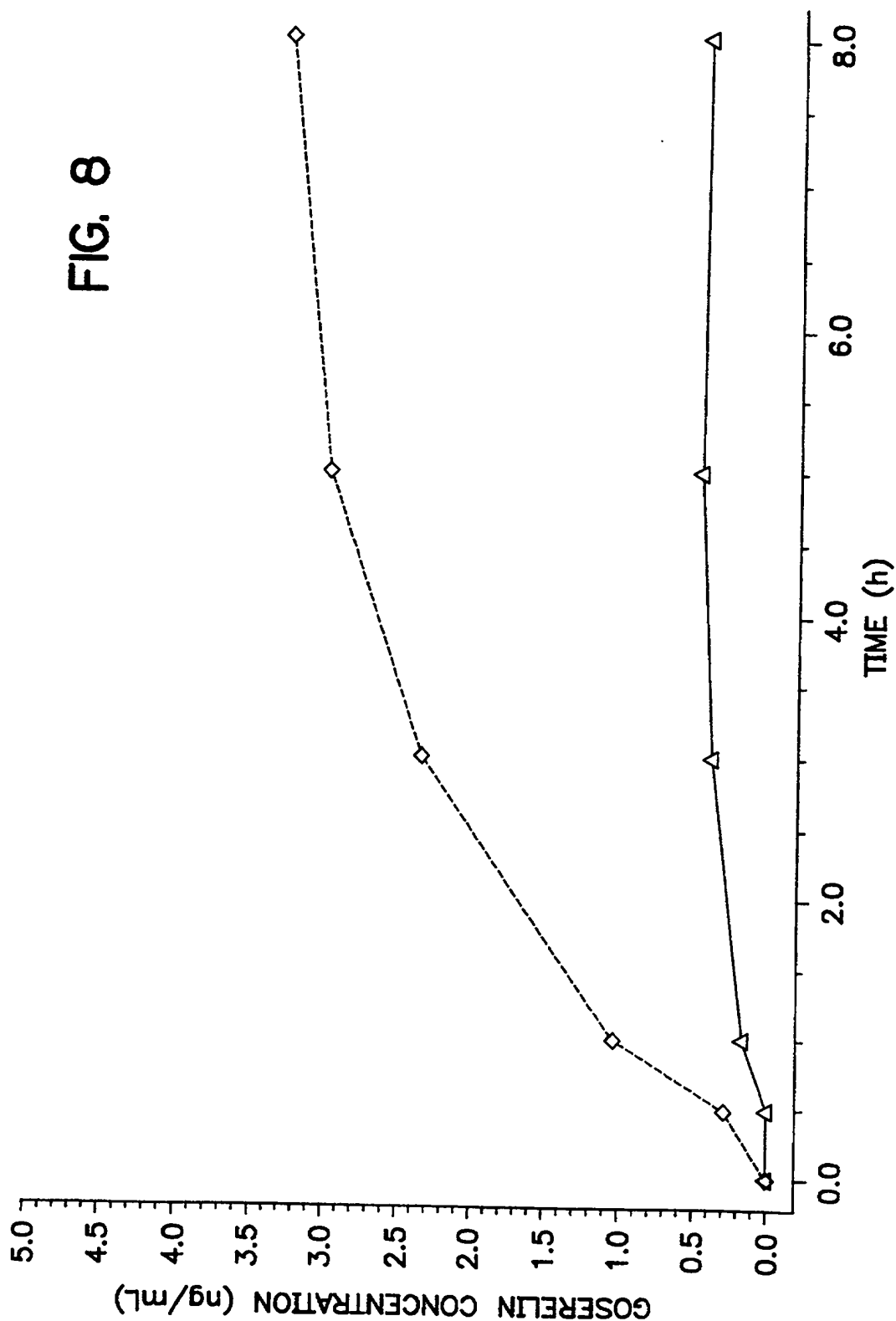
FIG. 7



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FIG. 8



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OO10/PTO Rev. 12/95	US Department of Commerce Patent and Trademark Office	<b>Attorney Docket Number</b> ARC 2426 CIP1
<b>DECLARATION</b>		<b>First Named Inventor</b> PHIPPS, Bradley J., et al
<input checked="" type="checkbox"/> Declaration Submitted with Initial Filing    OR <input type="checkbox"/> Declaration Submitted after Initial Filing		<b>COMPLETE IF KNOWN:</b>
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As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ELECTROTRANSPORT AGENT DELIVERY METHOD AND APPARATUS**

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY 07/06/96 as United States Application Number or PCT International

Application Number PCT/US96/10128 and was amended on (MM/DD/YYYY) (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119 (a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

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☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

## DECLARATION

Page 2

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

US Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
	PCT/US96/09989	06/07/96	

☐ Additional US or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Firm Name: ALZA Corporation

Payor  
Number: 01-1173  
(if applicable)

Name	Registration Number	Name	Registration Number
Steven F. Stone	<u>20,246</u>	D. Byron Miller	<u>30,661</u>
Paul L. Sabatine	<u>22,539</u>	John A. Dhuey	<u>26,265</u>
Michael J. Rafa	<u>38,740</u>	Christopher P. Rogers	<u>36,334</u>
		Pauline Ann Clarke	<u>29,783</u>

☐ Additional attorney(s) and/or agent(s) named on a supplemental sheet attached hereto.

☒ Please direct all correspondence to:

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Christopher P. Rogers

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Name of Sole or First Inventor:

J. Bradley Phipps

☐ A petition has been filed for this unsigned inventor.

Given

Name: J.

Middle

Initial: B.

Family

Name: Phipps

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Inventor's

Signature:

Date:

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Applicant

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☒ Additional inventors are being named on supplemental sheet(s) attached hereto.



DECLARATION				ADDITIONAL INVENTOR(S) Supplemental Sheet	
Name of Additional Joint Inventor, if any: Gary A. Lattin				<input type="checkbox"/> A petition has been filed for this unsigned inventor.	
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Inventor's Signature: <i>[Signature]</i>				Date: November 9, 1997	
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Name of Additional Joint Inventor, if any: Suneel K. Gupta				<input type="checkbox"/> A petition has been filed for this unsigned inventor.	
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<input type="checkbox"/> Additional inventors are being named on supplemental sheet(s) attached hereto.					